JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2024; 8: 750-758
https://doi.org/10.30621/jbachs.1084860
RESEARCH ARTICLE

IS THE OCCURRENCE OF GESTATIONAL DIABETES MELLITUS IN PREGNANCIES HIGHER FOLLOWING IN VITRO FERTILIZATION TREATMENT? WHY? A RETROSPECTIVE COHORT STUDY

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Received: 04.09.2024; **Accepted:** 26.09.2024; **Available Online Date:** 30.09.2024

Cite this article as: Aypar-Akbağ NN, Aluş-Tokat M, Özöztürk S, Ünsal-Avdal E, Okyay RE, Doğan OE. Is the occurrence of Gestational Diabetes Mellitus in pregnancies higher following In Vitro Fertilization treatment? Why? A retrospective cohort study. J Basic Clin Health Sci 2024; 8: 750-758.

In accordance with the decision (Decision No: 4), made at the meeting of the Scientific Research and Publication Ethics Committee of Dokuz Eylül University Health Sciences on 03 April 2023, an ethical review had been initiated pursuant to Article 9 of The Council of Higher Education (YÖK) Publication Ethics Directive for the article titled "Is the Occurrence of Gestational Diabetes Mellitus in Pregnancies Higher Following in Vitro Fertilization Treatment? Why? A Retrospective Cohort Study," published in the Journal of Basic and Clinical Health Sciences with the citation details '2023; 7: 94-102. https://doi.org/10.30621/jbachs.1084860'. Upon completion of the review, the Committee decreed that no ethical violation was found in the article at its meeting held on 25 April 2024 (Decision No: 2). In light of this final decision, the previously retracted article has been republished in our journal with the new citation details '2024; 8: XX-XX. https://doi.org/10.30621/jbachs.1543485'.

ABSTRACT

Purpose: This study aim to determine the occurrence of gestational diabetes mellitus (GDM) in pregnancies after IVF treatment and to evaluate the factors that reduce this risk.

Material and Methods: This retrospective cohort study was conducted using the medical records of pregnant women who conceived following IVF at the in-vitro fertilization center between 2002–2019. The data were obtained from medical records and phone interviews. Univariate and multivariate logistic regression analyses were performed.

Results: The incidence of GDM was found to be 16.7%. The regression model indicated that the risk of GDM was 4.57 times higher in the age group 36–40 at conception during the IVF cycle than the age group 31–35 (95% CI = 1.18–17.73, p = .028). Furthermore, women who conceived after the second IVF trial had a risk of GDM 3.464 times higher than those that conceived after their first IVF trial (95% CI = 1.07–11.23, p= .038).

Conclusion: As age and number of IVF trials increase in infertile women, the risk of GDM increases after IVF treatment.

Keywords: Gestational diabetes mellitus, in vitro fertilization, risk factors

INTRODUCTION

The lack of consensus on screening standards in countries across the world causes problems in comparing the prevalence of gestational diabetes mellitus (GDM) (1). However, it is reported that 21.1 million pregnant women worldwide are affected by hyperglycemia and 80.3% of them have GDM (2). Although the reported prevalence rates in Turkey (7.7%) are less compared to the rest of the world (in Europe 19%, in South-East Asia 24%), they have been increasing over the years (3). Therefore, Turkey is considered a priority country in the world regarding the prevention of diabetes. These rates for GDM, which cause serious health problems for both mothers and babies in the world and in Turkey, are alarming (4).

From the evaluation of the increasing rates, it is understood that the most important risk factors for occurrence of GDM are family history, advanced maternal age, obesity (5,6). It is also known that the hormones used to treat infertility can lead to disorders in lipid, carbohydrate, and protein metabolism and cause diabetes post IVF (7-16). The fact that the use of IVF has increased up to 4.1% in recent years in our country (17) indicates that it presents a significant risk for GDM.

In a study conducted by Ashrafi et al. (2014) evaluating GDM risk, it was reported that the incidence of GDM was higher in women who became pregnant after IVF treatment compared to those who were pregnant without it. Similar studies also found a high risk of GDM after IVF (13,14). However, it was also observed that many factors that exist before pregnancy also affect the occurrence of complications in pregnancies through IVF (11,18). Hormones used in IVF affect women's conception processes as well as pregnancy and post-natal processes. This study therefore aims to determine the development of GDM in women who conceived after IVF and identifies the factors that can improve this risk.

MATERIAL AND METHODS

Study Design

This study designed as the retrospective cohort study.

Setting and Sample

The population of the retrospective cohort study comprised women who had undergone IVF treatment in the in-vitro fertilization center of at Dokuz Eylul University Hospital in Izmir and had conceived between 2002–2019. The sample size was not calculated since it was intended to reach the entire population. The study inclusion criteria were the following: BMI level between 18 and 25 kg/m2, conception after IVF, and having a single fetus. Confusing factors such as the following were excluded from this study: BMI over 25 kg/m^2, polycystic ovary syndrome (PCOS), and multiple pregnancy conditions developed after treatment, maternal age of 40 years and over, having glucose intolerance or using a hypoglycemic drug, GDM history, stillbirth history, missed abortion history, given birth to a baby with a weight of 4000 grams and above (macrosomia), chronic diseases (hypertension, cardiovascular diseases, untreated thyroid disease, liver diseases, kidney diseases, autoimmune diseases, connective tissue diseases, among others) and a history of corticosteroid treatment. All women receiving the IVF treatment at this center used an equal dose of Human Chorionic Gonadotropin (HCG) injection during the ovulation period and vaginal progesterone treatment after embryo transfer. In total, 621 women conceived and gave birth in the mentioned timeframe. However, 369 women were not included in the study because they met at least one of the exclusion criteria. Therefore, a total of 252 pregnant women were included. Furthermore, 83 women could not be reached probably due to change in phone numbers over time and 43 registered women did not answer the phone calls; so they were excluded from the sample. Additionally, 18 women refused to participate in the research. Ultimately, a total of 108 women among the 252 could be reached. The post-hoc statistical power analysis was used to calculate the sample size. Using the G-power 3.1.9.4 program, the sample size was indicated to have 95% sufficient statistical power with 108 women (Effect size = 0.15; Alpha err prob = .05).

Tools

It was used that the using tools prepared in line with the literature review (7,8,10,13,14).

Phone Interview Form: The questions in this form were directly asked to women during telephone interviews. The number of gravidas, parity, birth week, and age at conception during IVF cycle comprised obstetric information included in the form. All participants reported that fasting glucose was measured in first trimester. Moreover, those diagnosed with GDM reported the use of the same

standard screening at 24–28 weeks of gestation by using a 75 mg oral glucose challenge test (OGTT) with abnormal blood sugar (> 92 mg/dl fasting values, > 180 mg/dl 1 hour after the start of a meal or > 153 mg/dl 2 hours after the start of a meal) during measurement (19). Finally, it was asked whether GDM was observed during their pregnancy.

Clinical Patient Medical Records: The questions in the section on fertility treatment were obtained from the medical records in the clinic by checking names, last names, and ID numbers of the women included in the study. Information such as the cause of infertility, type of medication used for ovulation induction, total dose of medication, and status of progesterone use after embryo transfer were taken from the "Clinical Patient Medical Records".

Data Collection

This study was conducted between May-July 2019. Initially, a list of women who gave birth after IVF was created from medical records and they were called by phone in order. Interviews were held with corporate phone tools and lasted an average of 15 minutes. During the interviews, brief information about the research was provided and verbal consent was obtained. Women who satisfied the inclusion criteria and who agreed to participate in the research were interviewed. Besides the response from participants, GDM diagnosis was confirmed by checking patient information from the clinical database. The information about medications used for ovulation induction and after embryo transfer for supporting the luteal phase was obtained from the patient's medical records in the clinic; these were evaluated in detail.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics for Windows, Version 22.0. Descriptive statistics for some infertility and obstetric characteristics were presented as mean ± standard deviation ($\bar{x} \pm SD$) or number (percent). First, the logistic regression model was created by taking GDM diagnosis as the dependent variable and the obstetric and infertility treatment characteristics as independent variables. Second, independent variables with statistical significance ($p < .05$) in the model were included in the multiple bivariate logistic regression model. The Backward Wald method was used to determine the variables that would remain in the final model. Furthermore, odds ratio (OR) and 95% confidence intervals (95% CI) were estimated. Additionally, we accepted $p < 0.05$ as statistically significant.

Ethical Consideration

The study, approved by the non-invasive Research Committee of Dokuz Eylul University ((Date: 17.04.2019, Decision no: 2019/10–23)).

RESULTS

The Incidence of Gestational Diabetes Mellitus After IVF

The incidence of GDM in pregnancy after In Vitro Fertilization was determined as 16.7% (Table 1).

Table 1 The Incidence of Gestational Diabetes Mellitus in Pregnancy after In Vitro Fertilization (n=108)

GDM status developed in women	n	%
Yes	18	16.7
No	90	83.3

Abbreviation:GDM = Gestational Diabetes Mellitus.

Obstetric and Fertility Treatment Characteristics of Participants

The age at conception during IVF cycle was classified according to change in fertility status with age in the literature (19) as 20–30 years (n = 44, 40.7%), 31–35 years (n = 44, 40.7%) and 36–40 years (n = 20, 18.5%).

This study found that GDM occurrence rate in women who had their first IVF trial was 55.6%. Regarding the ovulation induction medications, three types of medical treatment were applied: the recombinant Follicle Stimulating Hormone (rFSH) (n = 76, 70.4%), Human Menopause Hormone (hMG) (n = 18, 16.7%), or rFSH and hMG combination (n = 14, 13.0%) (Table 2).

Factors Affecting Gestational Diabetes Mellitus Incidence After IVF

The factors affecting the incidence of Gestational Diabetes Mellitus after IVF were evaluated using the univariate logistic regression analysis (Table 3).

The variables age at conception during IVF trial and number of IVF trials, which were found important with univariate logistic regression analysis, were included

in the multivariate bivariate logistic regression analysis as well. Both variables included in the final model were found significant. Observing the final model, the risk of GDM in the age group 36–40 at conception during the IVF trial was found 4.566 times higher than the age group 31–35 (OR = 4.57, 95% CI = 1.18–17.73, p = .028). Additionally, women who conceived after second IVF trial had a risk of GDM 3.46 times higher than those who conceived after their first IVF trial (OR = 3.46, 95% CI = 1.07–11.23, p = .038) (Table 4).

DISCUSSION

The Incidence of Gestational Diabetes Mellitus After IVF

Different pregnancy complications after IVF are common. In a meta-analysis study, it was found that women who had conceived through the assisted

Table 2. Obstetric and Fertility Treatment Characteristics of Women Conceived after In Vitro Fertilization

	GDM group (n=18) n (%)	Non-GDM group (n=90) n (%)	Total (n=108) n (%)
Age at conception during IVF cycle			
20-30 age	6 (33.3)	38 (42.2)	44 (40.7)
31-35 age	5 (27.8)	39 (43.3)	44 (40.7)
36-40 age	7 (38.9)	13 (14.4)	20 (18.5)
Gravida			
Primigravida	13 (72.2)	74 (82.2)	87 (80.6)
Multigravida	5 (27.8)	16 (17.8)	21 (19.4)
Parity			
Primiparity	18 (100)	82 (91.1)	100 (92.6)
Multiparity	0 (0)	8 (8.9)	18 (7.4)
The infertility factor			
Female	5 (27.8)	21 (23.3)	26 (24.1)
Male	9 (50.0)	35 (38.9)	44 (40.7)
Female and Male	0 (0)	1 (1.1)	1 (.9)
Unexplained	4 (22.2)	33 (36.7)	37 (34.3)
Female infertility factor			
Anovulation	1 (5.6)	8 (8.9)	9 (8.3)
Endometrial factors	1 (5.6)	6 (6.7)	6 (5.6)
DOR	2 (11.1)	2 (2.2)	6 (5.6)
Tubal factor	1 (5.6)	6 (6.7)	6 (5.6)
Number of IVF trials			
1	10 (55.6)	71 (78.9)	81 (75.0)
2	7 (38.9)	15 (16.7)	22 (20.4)
3	1 (5.6)	4 (4.4)	5 (4.6)
Ovulation induction drugs			
rFSH	11 (61.1)	65 (72.2)	76 (70.4)
HMG	3 (16.7)	15 (16.7)	18 (16.7)
rFSH + HMG	4 (22.2)	10 (11.1)	14 (13.0)
Vaginal progesterone for luteal phase support			
Yes	11 (61.1)	60 (66.7)	71 (65.7)
No	7 (38.9)	30 (33.3)	37 (34.3)
	x̄±SD	**x̄±SD**	**x̄±SD**
Drug starting dose (unit kg / day)	245.13 ± 144.83	260.55 ± 103.70	257.98 ± 110.95
Drug total dose (unit kg / day)	2966.66 ± 2249.28	2763.63±1256.81	2797.47 ± 1457.20
Drug use time (days)	11 ± 2.56	18 ± 10.52	10.60 ± 1.92

Abbreviations: DOR = Diminished Ovarian Reserve; GDM = Gestational Diabetes Mellitus; HMG = Human Menopause Hormone; rFSH = Recombinant Follicle Stimulating Hormone.

Table 3. Variables Predictive of The Occurrence of Gestational Diabetes Mellitus in Pregnancies after In Vitro Fertilization: Univariate Logistic Regression Analysis

	β	S.E.	Wald Statistics	p	OR	95% CI	
						Lower	Upper
Age at conception during IVF cycle							
31-35 age	Ref						
20-30 age	.21	0.65	0.10	.748	1.23	0.35	4.38
36-40 age	1.44	0.67	1.62	.032*	4.20	1.14	15.54
Gravida							
Primigravida	Ref						
Multigravida	.58	0.59	0.94	.332	1.78	0.56	5.70
Parity							
Primiparity	Ref						
Multiparity	-.11	0.57	0.04	.851	0.90	0.29	2.78
The infertility factor							
Unexplained	Ref						
Female	.68	0.73	0.86	.353	1.96	0.47	8.16
Male	.75	0.65	1.35	.246	2.12	0.60	7.56
Female and Male	-	-	-	-	-	-	-
Number of IVF trials							
1	Ref						
2	1.20	0.57	4.44	.035*	3.31	1.09	10.10
3	.57	1.17	0.24	.623	1.78	0.18	17.51
Induction drugs							
rFSH	Ref						
HMG	.17	0.71	0.06	.814	1.18	0.29	4.77
rFSH + HMG	.86	0.68	1.62	.203	2.36	0.63	8.88
Vaginal progesterone for luteal phase support							
Yes	Ref						
No	.24	0.53	0.21	.651	1.27	0.45	3.62
Drug starting dose	-.00	0.00	0.29	.589	0.99	0.99	1.00
Drug total dose	.00	0.00	0.29	.589	1.00	1.00	1.00
Drug use time	.12	0.13	0.91	.339	1.13	0.88	1.44

Table 4. Variables Predictive of The Occurrence of Gestational Diabetes Mellitus in Pregnancies after In Vitro Fertilization: Multivariate Bivariate Logistic Regression Analysis*

	β	S.E.	Wald Statistics	p	OR	95% CI	
						Lower	Upper
Constant	-2.51	0.56	20.02	.001**	0.09		
Age at conception during IVF cycle							
31-35 age	Ref						
20-30 age	.40	0.67	0.35	.555	1.49	0.40	5.51
36-40 age	1.52	0.69	4.81	.028***	4.57	1.18	17.73
Number of IVF cycles	Ref						
1	1.20	0.60	4.29	.038***	3.46	1.07	11.23
2	.57	1.21	0.22	.636	1.77	0.17	18.81
3							

*Multivariate bivariate logistic regression analysis results (Variables included in the model: Age at conception during IVF cycle, number of IVF cycles); **p < .001, ***p < .05.

reproductive technology (ART) method and who had a single fetus, experienced complications such as preeclampsia, GDM, placenta previa, ablatio placentae, antepartum hemorrhage, polyhydramnios, and oligohydramnios (14). In studies conducted at different times, the common complication was GDM, and it was determined that the risk increased by 1.99 times in pregnancies after ART (11-15,21). However, in our study, potential confounding factors were controlled with exclusion criteria to eliminate situations that are generally seen as risk factors in GDM.

In the current retrospective cohort study, it was found that GDM developed in 16.7% of pregnant women after undergoing infertility treatment. However, according to this result, the incidence of GDM in women who conceived after IVF were quite higher than our national GDM incidence (7.7%) (3) and this has a meaningful clinical importance. Similarly, in other studies that evaluated the pregnancy outcomes in Canada (11.2%) and Singapore (30.3%), it was stated that a high rate of GDM were developed after infertility treatment (9,15). The meta-analysis studies conducted in recent years showed that GDM is affected by the use of ART (16,22). In a meta-analysis conducted by Mohammadi et al., It was shown that those who became pregnant with ART developed 1.51 times more GDM than those who conceived spontaneously (16). The different medical ovulation induction protocols used in the ART procedure may have influenced the increased likelihood of GDM. Moreover, it is known that progesterone affects blood sugar by increasing insulin resistance (12). Therefore, the use of progesterone for luteal phase support in all ART cycles as well as in the first trimester of pregnancy might be a possible explanation for the increased risk of GDM.

Affecting Factors of Gestational Diabetes Mellitus Incidence After IVF

In the current study, data analysis based on a univariate logistic regression and multiple bivariate logistic regression model provides us a comprehensive understanding of the relationships underlying all potential determinants of the occurrence of GDM. The risk of GDM in women at age group 36–40 during conception with IVF cycle was 4.57 times higher than the age group 31–35. This finding indicates that age at conception during IVF trial plays an important role for GDM risk. Similarly, previous research studies have demonstrated that as the age increases in infertility treatment, the rate of GDM complications in pregnancy may increase (12,23-25). In a study conducted by Moaddab et al. (2017) evaluating the GDM incidence in women who had conceived through the ART method, it was found the highest risk group was women between 45 and 50 years of age with the incidence of GDM being 13.9% (24). Changes in women's metabolic activities should be considered as age increases. It is known that increased risks in advanced-age pregnancies will continue in the pregnancies through ART as well, and certain factors such as medication used and stress can increase the risks in the process.

However, the number of gravida and parity of women receiving IVF treatment did not affect the incidence of GDM. Similar to the current research results, Wang et al. (2013) stated that gravida and parity numbers were not effective in terms of GDM risk in women who had conceived through ART. The stress experienced due infertility negatively affects the fertility of women regardless of the cause behind the infertility (26,27). Moreover, social pressure for having a child that is common in Turkish culture can increase this stress. A successful treatment process resulting in childbirth reassures women that at least this burden is removed. It is thought that this might reduce the risk of GDM brought about by IVF.

The cause of infertility and type of female factor did not have an impact on the risk of occurrence of GDM in women who conceived through IVF. Similarly, in a retrospective evaluation of two groups with and without GDM who had conceived through the ART method, any difference between the groups in terms of causes of infertility was not found (23). In a study evaluating the incidence of pregnancy complications in ART group, it was stated that PCOS (12.8%) being the cause of infertility caused insulin resistance (28). In our study, risk factors in GDM that increase insulin resistance were not included to eliminate potential confounding factors and represent the influence of IVF treatment. Therefore, factors that are accepted as the cause of infertility but that do not cause insulin resistance do not influence the increase in the incidence of GDM.

The number of IVF trials explained a significant proportion of GDM occurrence rate in women. The women who conceived after the second IVF trial had higher GDM incidence than those who conceived after their first IVF trial. Factors such as undergoing infertility treatment many times, repeatedly entering an unknown process and experiencing failures can

increase the stress level of women. This may be associated with the increase in blood glucose level (29). In addition to these situations, as the number of trials increase, the ovulation induction and the duration of exposure to these drugs also increase. Therefore, it is necessary to assess and inform women about GDM risk, encourage them to share their experiences, and provide information to clarify any uncertainty.

In the current study, it was determined that induction drugs, drug starting dose, total dose, and use duration of medication for ovulation induction during treatment was not statistically different in groups with and without GDM. Similarly, in different studies, it was found that the drugs used in IVF treatment (gonadotropin hormone agonist, hCG) had no effect on insulin resistance and lipid metabolism (30) and did not increase the incidence of GDM (26,31). However, contrary to these studies, in a prospective population-based cohort study performed with 3126 pregnant women who conceived after ART, it was found that as the drug dose used in the infertility treatment increased, risk of development of GDM increased (28). This difference might be due to the sampling size and feature and the proportion of women with a history of PCOS (12.9%). In our results, although the drug dose did not affect the development of GDM, a higher risk of GDM in women who had a second IVF trial was found compared to those who conceived after the first IVF trial; this may be associated with more exposure to induction drugs.

Another finding of the current study was that using vaginal progesterone after embryo transfer was also not an influential factor in the development of GDM. In the study conducted by Zipori et al. (2018), vaginal progesterone used daily for preventing abortion caused changes in the glucose tolerance test, but there was no significant effect on GDM diagnosis (32). In another study supporting Kouhkan et al. (2018), it was determined that the administration of injectable progesterone (ART) increased the risk of GDM approximately twofold compared to vaginal progesterone in single pregnant women following ART (23). In the country where the current study was conducted, while vaginal progesterone is routinely administered to every woman after ART, in spontaneous pregnancies, it is used only by women who have a risk of abortion. The result of this study regarding the effect of progesterone on GDM risk may be explained by the combination of routine practice and a lower risk of vaginal progesterone in the literature compared to intramuscular progesterone.

Our study has some limitations. The major limitation is the lack of a control group. GDM risk factors were determined as exclusion criteria at the beginning of the study. And, all women received progesterone therapy. Therefore, a control group could not be formed during the IVF treatment process. The second limitation was that although the number of people receiving treatment in the institution was high within the selected time period, a significant number of women could not be reached, and the data were accessed via the telephone registered in the institution. This may be due to the lengthy treatment process of some women and their contact information changing over time. Therefore, the sample size was limited. Moreover, the external validity of our results needs to be confirmed as the study was conducted in a single IVF center. Therefore, it is recommended that studies be conducted in other clinics with similar IVF procedures. Finally, as this study used a retrospective design, we cannot ensure that all information related to the past was recorded or remembered properly by the women. Therefore, the results of the current study should be validated with a prospective cohort and multicenter research.

CONCLUSION

The results of current research indicate that the risk of GDM after IVF treatment increases with age. Therefore, women who become pregnant with IVF at 35 years or above should be evaluated more carefully in terms of GDM and should undergo a controlled antenatal process. Furthermore, the increase in the risk of GDM as the number of IVF trials increased was found important in terms of IVF trail management. Women should be encouraged to share their feelings and thoughts to reduce their stress at the beginning of every IVF treatment cycle. Fertility and obstetrics nurses and doctors can play a vital role in early risk evaluation and can encourage healthy diet and physical activity to prevent excessive weight gain and development of GDM during pregnancy. In this manner, it is believed that healthy pregnancies and babies can contribute to the health system in the country and decrease health expenditures. In further studies, GDM prevalence and risk factors should be compared with pregnant women who conceived spontaneously and after IVF in a similar age group.

Acknowledgement: None.
Author contribution: Conception: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S, Ünsal Avdal E, Okyay RE, Doğan ÖE. Design: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S, Ünsal Avdal E, Okyay RE, Doğan ÖE. Supervision: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S. Fundings: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S. Materials: Aypar Akbağ NN, Özöztürk S. Data Collection and/or Processing: Aypar Akbağ NN, Özöztürk S. Analysis- Interpretation: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S. Literature Review: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S, Ünsal Avdal E, Okyay RE, Doğan ÖE. Writing: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S, Ünsal Avdal E, Okyay RE, Doğan ÖE. Critical Review: Aypar Akbağ NN, Aluş Tokat M, Özöztürk S, Ünsal Avdal E, Okyay RE, Doğan ÖE.
Conflict of interest: The authors declare that they have no conflicting interests.
Ethical approval: Approval was gained for ethical compliance from the Non-invasive Research Ethics Committee of the Dokuz Eylul University (Date: 17.04.2019, Decision no: 2019/10–23).
Funding: No funding was received for this study.
Peer-review: Externally peer-reviewed.

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